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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-2 4-26* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's arguments with respect to claims 1-14, 20-23 and 27 have been considered but are moot in view of the new ground(s) of rejection. Additionally, the indicated allowability of claims 24-26 is withdrawn in view of the new grounds of rejection set forth below.

Response to Amendment

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-2, 4-14, and 20-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter)

The instant claims recite "wherein said compound specifically hybridizes with nucleotides 1-114 or nucleotides 151-14121 as set forth in SEQ ID NO: 3 and inhibits the expression of a nucleic acid molecule encoding apolipoprotein B." As support for this amendment, Applicants referred to page 9, and pages 90-91 (Table 1). However, nowhere in the specification as filed is the range 1-114 or 151-14121 adequately supported. Table 1, provides support for the end points of the recited ranges, however the Table does not suggest the design of antisense oligonucleotides targeting all of the nucleotides encompassed by the claimed range. In particular, note that the antisense

oligonucleotide of SEQ ID NO: 20, targets nucleotide 114, however there is no antisense inhibition noted for this particular antisense oligonucleotide. According to the claim, the compound functions to specifically hybridize and inhibit the expression of apolipoprotein B. There are multiple examples of this, again, for example note the antisense compound according to SEQ ID NO: 24 of the instant application, this antisense compound targets nucleotide 451, included within the range of 151-14121, however this antisense compound does not display any inhibitory effect against apolipoprotein B mRNA expression. The nucleotide ranges according of 1-114 and 151-14121 of SEQ ID NO: 3, set forth in the claims are considered new matter since the specification as filed does not provide proper antecedent basis for these limitations.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-2, 4-14, and 20-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (WO 01/12789 A2) in view of Branch, Monia et al., and Agrawal et al. for the reasons of record set forth in the Office Action mailed 1-13-04.

6. Applicant's arguments filed 5-13-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the claimed subject matter as a whole is not suggested by the combined disclosures relied on by the Examiner and nothing in these disclosures suggests that the primary reference can or

should be modified to provide the invention as claimed. According to Applicants, everything in the Chan et al. reference is directed to ribozymes, which are a distinct class of molecules compared to the claimed compounds. Applicants point out how the ribozymes of Chan et al. differ from the non-catalytic compounds of the instant invention. In particular, Applicants state that catalytic site of the ribozymes of Chan et al. is not complementary to and cannot hybridize to the target nucleic acid. Additionally, Applicants state that the non-catalytic antisense molecules of the instant invention tend to hybridize to the target nucleic acid over its entire length depending on the degree of complementarity.

Contrary to Applicant's assertions, it is noted that ribozymes are generally known in the art as comprising binding arms that specifically bind to the target nucleic acid molecule around the cleavage site. Therefore, if the cleavage site of the RB15 ribozyme of Chan et al. targets nucleotide 6679, the ribozyme would be designed to comprise binding arms that are complementary to nucleotides that surround this site. It is noted that the flanking sequence of position 6679 are encompassed within the nucleotide range 151-14121 of SEQ ID NO: 3 as set forth in the instant claims. See page 2 of Chan et al., that clearly states that the ribozymes of Chan et al. comprise two flanking segments 8 to 50 (and preferably 10-20) bases in length, that are complementary to a nucleotides sequence encoding apoB100 mRNA. Although, Chan et al. does not specifically disclose non-catalytic compounds of 8 to 50 nucleobases in length that specifically hybridizes with nucleotides 1-114 or nucleotides 151-14121 as set forth in SEQ ID NO: 3, Chan et al. provides motivation for designing nucleic acid based inhibitors for the express

purpose of inhibiting the expression of nucleic acid encoding Apolipoprotein B mRNA, the sequence of which is known in the art, see GenBank Accession No. X04506.

Furthermore, since the prior art provides express motivation for designing inhibitors of apolipoprotein B mRNA, and provides the nucleic acid sequence of apolipoprotein B, one of skill in the art seeking to further understand the function of apolipoprotein B would have been motivated to design antisense compounds targeting apolipoprotein B mRNA. As stated previously, Agrawal et al. generally states (regarding the feasibility of utilizing antisense technology), "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years." Moreover, the prior art (see Monia et al. and Branch) provides extensive guidance for designing antisense compounds targeting a nucleic acid molecule with a known sequence.

Moreover, absent evidence of unexpected results, it would have been obvious to one of ordinary skill in the art at the time invention was made to modify the teaching of Chan et al. with the teachings of Branch, Monia et al. and Agrawal et al. in the design of the present invention. Chan et al. provide explicit disclosure and motivation for designing a nucleic acid based inhibitor of ApoB mRNA expression. As stated previously, one of ordinary skill in the art seeking to further understand the role of apolipoprotein B gene expression in cellular processes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the *apolipoprotein B* gene, since according to Agrawal, if the sequence of a gene is known, designing antisense oligonucleotides to target that gene would allow the ordinary skilled artisan to further explore and understand the function of that particular gene. Moreover, it would have

been obvious at the time the invention was made to substitute the ribozymes targeting apolipoprotein B mRNA with the non-catalytic antisense compounds according to the present invention, since ribozymes and antisense compounds are both nucleic acid based inhibitors, and both function to reduce the expression of a target mRNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute one functionally equivalent nucleic acid based inhibitor for another that is to be used for the same purpose, namely for inhibiting the expression of apolipoprotein B mRNA.

Moreover, one of ordinary skill in the art would have been motivated to design antisense oligonucleotides of about 17 nucleotides in length (see Branch) targeting Apo B and comprising the modifications taught by Monia et al. since modified oligonucleotides according to the preferred embodiments of Monia et al. possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides.

Applicant's arguments do not take the place of evidence, the instant claims remain rejected for the reasons of record.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE